REMARKS

The courtesies extended by Examiner Williamson with the representatives of the Applicants in the personal interview of July 16, 2001 is acknowledged with appreciation.

Currently, claims 1-75 are pending. Reconsideration of the application is respectfully requested.

I. Rejection Under 35 U.S.C. § 112

The rejection of the pending claims under 35 USC §112, first paragraph, is maintained in the instant Office Action on the grounds of non-enablement. Although the Examiner acknowledges that the specification enables a specific controlled release oral solid dosage form, *viz.*, a dosage form having the exemplified core composition and an outer coating having polymers at a specific weight ratio and combined weight, it is asserted that the specification does not enable a claim that does not expressly recite these limitations. The Applicants respectfully traverse.

As discussed during the July 16, 2001 personal interview, the Applicants maintain and reiterate:

(1) that there is ample support in the specification and known in the art which indeed enables a person of ordinary skill to make and use a broad range of controlled release formulations to attain the claimed pharmacokinetic parameters (with the benefit of the hindsight provided by the present application), including those that have not specifically been exemplified in the subject application; and

(2) that the Examiner's position with respect to the enablement issue conflicts with that taken with respect to the assertion of obviousness.

A. Enablement

With regard to the issue of adequate support provided in the specification, the Applicants submit that a variety of controlled release technologies are disclosed in and supported by the subject application. A person of ordinary skill in the art would be capable of modifying these disclosed technologies in order to adjust or manipulate the mean time to maximum concentration (T_{max}) of an alkyl ester of a hydroxy substituted naphthalene. In support of this position, the Examiner is again directed to page 19, line 36 of the application which recites the following:

> **Other controlled release technologies known to those skilled in the art can be used in order to achieve the controlled release formulations of the present invention**, i.e., formulations which provide a mean Tmax of the drug (i.e., a HMG-CoA reductase inhibitor) at a desired time after oral administration, ...and which preferably provide pharmacokinetic parameters described herein when orally administered to human patients. **Such formulations can be manufactured as a controlled oral formulation in a suitable tablet or multiparticulate formulation known to those skilled in the art.** (Emphasis added). In either case, the controlled release dosage form may optionally include a controlled release carrier which is incorporated into a matrix along with the drug (e.g., HMG-COA reductase inhibitors), or which is applied as a controlled release coating.

The instant application thus sets out a plurality of controlled release technologies, e.g., tablet matrix, beaded capsule, or the like, which can be modified to achieve the results of the claimed invention and the application is not limited to the formulations specifically recited in the Examples.

The Applicants submit that enablement must also be analyzed in view of what is known in the art. Therefore, the disclosure in the present application (namely, a dosage form which provides a mean (T_{max}) of the claimed active at about 10 to about 32 hours after administration) must be considered in view of other controlled release technologies that were well known at the time of filing the application. Once the desirable pharmacokinetic factors of the claimed active are determined, one of ordinary skill would be clearly enabled to practice the claimed invention directed to a dosage form that exhibits these parameters. These claimed parameters are also clearly enabled, as provided in the biodata of the application, e.g., at Tables 6-11 at pages 45-51.

In stating that without the outer coating of the core "the composition will not be controlled release", it appears that the Office Action asserts that a coating is required in order to provide a controlled release composition. Specifically, the Office Action states that "[t]he limitation...regarding the core and the coating as well as the ratio of pH sensitive polymer to insoluble polymer and the total weight used **are critical** to the invention." This is not the case, as the prior art is replete with controlled release technologies comprising an active agent in a matrix without the need for a further coating. The criticality of the subject invention resides in

the dosage form exhibiting the recited pharmacokinetic parameters, not the formulation itself. Thus, the core and coating, and ratios of the polymers are not critical to the invention.

B. Conflict between §112/§103 Rejections

As discussed in the interview, the Applicants assert that there is an inherent conflict between the enablement rejection under 35 U.S.C. §112, first paragraph, and the obviousness rejection under 35 U.S.C. §103(a). The Applicants respectfully submit that the claimed invention must be enabled if it is asserted to be obvious. Clearly, both rejections may not concurrently apply to the same claimed invention. In essence, the Examiner has created an estoppel to a non-enablement rejection, as he has taken the position that it would be within the abilities of one skilled in the art to make a controlled release fomulation of the claimed agents which exhibit the recited pharmacokinetic properties utilizing known controlled release technology. Accordingly, as presented during the interview and *agreed to* by the Examiner, the non-enablement rejection cannot stand in view of the Examiner's later grounds of rejection that the claimed subject matter is obvious over a combination of the cited references.

In summary, it is respectfully submitted that one skilled in the art has more than sufficient information to manufacture such formulations, without undue experimentation, utilizing the hindsight provided by the present application. It matters not whether such additional types of controlled release formulations were actually exemplified in the examples as there is no such requirement under U.S. law. Reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested upon reconsideration.

II. Rejections Under 35 U.S.C. § 103

The pending claims also stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Monaghan et al. (U.S. Patent No. 4,231,938) in view of Oshlack et al. (U.S. Patent No. 5,324,351 or 5,472,712). The Applicants respectfully traverse this rejection in that none of these references, taken alone or in combination, teach or suggest a controlled release dosage form containing the particular active ingredient and exhibiting the claimed pharmacokinetic parameters. Nor do the cited references teach or suggest a modification of their disclosed formulations such that the claimed parameters would be achieved.

In presenting the obviousness rejection, the Office Action states that Monaghan et al. disclose lovastatin which "may be administered orally or parenterally in the form of a capsule, a

tablet, an injectable preparation and the like..." but that "Monaghan et al. do not disclose the structure of the capsule, tablet, etc." The Office Action then cites Oshlack et al. for their disclosure of "compositions used to overcoat active agent including pharmaceuticals...to protect from the environment". It is then concluded that "it would have been obvious to one of ordinary skill in the art to use the coating compositions disclosed by Oshlack et al. in the invention of Monaghan et al. to obtain an active ingredient that is protected from the environment to provide stability..." (emphasis added).

In contrast to these assertions of obviousness, it must first be recognized that the claimed invention is not directed to an active ingredient in a formulation that serves to protect it from the environment for purposes of stability. Instead the subject invention is directed to controlled release dosage forms containing specific active agents which provide advantageous pharmacokinetic and pharmacodynamic characteristics. While stability is certainly a useful property, it is not the focus of the claimed invention.

The Monaghan et al. reference is directed solely to formulations comprising the drug lovastatin (and structurally related substances) which may be administered in a variety of different dosage forms and modes of administration. Monaghan et al. do not describe or suggest a need for a coating. Although, Oshlack et al. describe compositions used to coat active agents, including certain pharmaceuticals, there is no teaching or suggestion in either Oshlack et al. reference, to coat a composition comprising an alkyl ester of a hydroxylated naphthalene. Thus, at an initial level, there is no motivation to combine any of the cited references.

At a second level, even assuming arguendo that the references are properly combinable, once combined, the cited references fail to teach or suggest the claimed invention. By combining these cited references, one of ordinary skill in the art would not be presented with a teaching or suggestion of a once-a-day, controlled release dosage form of the specific class of actives with the claimed T_{max}. In support of this position, the Examiner is directed to the Oshlack '351 reference which does not provide any in-vivo data and the Oshlack '712 reference, which provides in-vivo data ranging from a T_{max} of 0.88 (table 43) to 7.8 (table 52). Further, the '712 references does not provide any motivation to modify the formulations therein to provide a T_{max} from about 10 to 32 hours of an alkyl ester of a hydroxylated naphthalene as recited in the present claims. For the sake of completeness, it is respectfully submitted that even if the Oshlack '712 did provide a T_{max} of about 10 to 32 hours (which it does not), the claimed invention would still be novel and unobvious as the T_{max} of one class of drugs provided by a formulation will not necessarily be the same T_{max} provided for another class of drug

incorporated in the same formulation. Further, a desirable T_{max} for one class of drug, is not necessarily desirable or beneficial for another class of drug.

IV. Information Disclosure Statements

The Examiner is requested to return the initialed PTO-1449 Form from the Information Disclosure Statement submitted March 6, 2001 which was not returned with the previous Office Action. For the Examiner's convenience, a duplicate copy of this PTO-1449 Form is enclosed.

The Examiner is also directed to the enclosed Information Disclosure Statement and PTO-1449 Form filed herewith.

V. Conclusion

It is now believed that the above-referenced rejections have been obviated and withdrawal is respectfully requested. It is believed that all claims are now in condition for allowance.

An early and favorable action is earnestly solicited.

Respectfully submitted,
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